CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

No. 345
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COMMITTEE:
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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
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Activated: 7/1/57
Extended to 9/1/58
Renewed: 9/1/58

APPLICATION FOR RESEARCH GRANT

Date: APRIL 4, 1962

1. Name of Investigator: DUANE G. WENZEL, PH.D.

2. Title: Professor of Pharmacology

3. Institution and Address: School of Pharmacy
University of Kansas
Lawrence, Kansas

4. Project or Subject: "A STUDY OF CENTRAL ACTIONS OF NICOTINE"

5. Detailed Plan of Procedure:

INTRODUCTION:

The use of tobacco induces a pleasurable feeling that can not be adequately described as "tranquilization" or "stimulation". There are indications that such an effect is related to the release of catecholamines, presumably within the brain itself. This evidence is not entirely adequate, for it has been related to nicotine-induced convulsions rather than to moderate signs of a central action. Such convulsions, however, are blocked not only by various adrenergic blocking agents, but by atropine-like compounds. This activity of the latter group indicates acetylcholine as the mediator affecting catecholamine release.

In view of the therapeutic value of amine oxidase inhibitors and the so-called psychic energizers in various depressive states, it is proposed that the central mechanism of nicotine, other than the convulsive effects, be more closely examined, particularly in reference to its potential interaction with various psycho-therapeutic agents.

Although nicotine has been frequently tested for various central actions, such tests have usually been based upon inadequate methodology and poor experimental design. In the tests to be outlined, adequate numbers of animals are to be employed with graded doses of nicotine, and the results are to be subjected to modern statistical analysis.

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In all tests where changes from control values are obtained, it is planned to repeat the study with the simultaneous administration of otherwise ineffective doses of an adrenolytic and a parasympatholytic agent. A monomine oxidase inhibitor will be similarly employed to observe possible potentiation of catecholamine-related effects.

A. SPONTANEOUS ACTIVITY

Nicotine is to be administered in the drinking water of separate groups of mice in doses corresponding to approximately 1/8, 1/2, and 2 packs of cigarettes per day for 20 weeks. Activity of all experimental groups and a control will be determined initially and at weekly intervals for the 20 week period. Activity measurements will be made with photoelectric cages. Groups demonstrating statistically different activity will be tested as previously indicated with an adrenalytic, parasympatholytic, and an amine oxidase inhibitor.

B. FALL TIME FROM A ROTATING ROD

Mice are to be chronically treated with nicotine as above. They are then to be administered reserpine and chlorpromazine in doses inducing a minimal change in fall time and observed for changes from the "reserpine control" and "chlorpromazine control" fall times.

C. PHYSICAL EFFICIENCY OR ENDURANCE

The effects of smoking upon physical efficiency has been widely studied in humans with equivocal results. It is proposed that mice chronically treated with nicotine be tested for their swimming endurance at weekly intervals over the 20 week test period. Again the mechanism of any change from control values would be sought.

D. PARKINSONIAN TREMOR

A parkinson-like reaction from large doses of reserpine has been thought to be related to the release of brain dopamine. As nicotine has been employed to induce tremors in experimental animals, the potential interaction of reserpine and nicotine in this effect will be tested with rabbits and rats.

E. STARTLE REACTION

Rats chronically treated with nicotine are to be compared with controls for the magnitude of the "startle reaction". An auditory stimulus is to be provided by a pistol shot and the magnitude of the response related to displacement of a spring-mounted cage.

F. EMOTIONAL REACTIVITY

Rats of the previous test (E) would also be observed to determine alterations in emotional reactivity. Using a rating scale of 0 to 4, as proposed by others, the following would be evaluated: resistance to capture in home cage, resistance to handling, muscular tension, squealing and vocalization, urination and defecation, aggressive reaction to forceps close to snout, and aggressive reaction to prodding.

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G. LSD-INDUCED BEHAVIORAL CHANGES

LSD in experimental animals induces characteristic alterations in behavior. Such alterations may be blocked or modified with suitable psychotherapeutic agents. Modification of such LSD effects by nicotine would be initially studied in the Siamese fighting fish and guppies, and in chronically-treated mice. Further studies may be called for in the presence of nicotine-induced modifications.

It is proposed that the above studies constitute an initial exploration of the central actions of nicotine. Contingent upon the results obtained, further work may be called for using more complex animal behavioral responses.

6. Budget Plan:

a.	Salaries	$6,200.00
b.	Expendable Supplies	800.00
c.	Permanent Equipment	400.00
d.	Overhead (15% of a,b,e)	1,095.00
e.	Other	300.00
	TOTAL	8,795.00

7. Anticipated Duration of Work: ONE YEAR, June 1, 1962 through May 31, 1963.

8. Facilities and Staff Available:

FACILITIES: Several modern air-conditioned pharmacology laboratories and animal quarters are available for the conduct of this study. The usual items of pharmacological equipment and a number of specialized pieces of apparatus are available should the problem expand beyond the original concepts.

STAFF: The project director will personally initiate and conduct this study during the summer of 1962. A pharmacologically trained research associate and two laboratory technicians are to directly work on the project and continue it throughout the year under the project directors supervision.

9. Additional Requirements: NONE

10. Additional information(including relation of work to other projects and other sources of supply):

The methods employed in the proposed study have been used by the director of the project and he is familiar with the pharmacological effects of nicotine upon experimental animals in the doses to be used.

The following references are related to testing methods or nicotine studies by the project director.

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1. Antispasmodic and Related Pharmacological Actions of Some gamma-Arylpropylamines, J. Am. Pharm. Assoc., 45, 414 (1956).

2. Central Stimulating Properties of Some Terpenones, Ibid., 46, 77 (1957).

3. The Effect of Nicotine on Experimental Hypercholesterolemia in the Rabbit, Ibid., 47, 338 (1958).

4. The Effect of Nicotine on Hyperchloesterolized Cockerels, Ibid., 48, 115 (1959).

5. The Relative Reliability of the Escape Reaction and Righting-Reflex Sleeping times in the Mouse, Ibid., 48, 90 (1959).

6. Effect of Nicotine on Cholesterol-Induced Atherosclerosis in the Rabbit, Circ. Res., 1, 256 (1959).

7. Cardiovascular Interaction of Nicotine, Ergonovine and Hypercholesterolemia in the Rabbit, Circ. Res., 9, 694, (1961).

8. Effects of Centrally-Acting Drugs on Human Motor and Psychomotor Performance, J. Pharm. Sci., in press.

Signature DUANE G. WENZEL
Director of Project
Professor of Pharmacology

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